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PATENT

Attorney Docket No.: A-68087-1/RMS/DCF/AMS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MARK CHEE et al.

Serial No. 09/425,633

Filed: October 22, 1999

For: SEQUENCE DETERMINATION OF NUCLEIC ACIDS USING ARRAYS WITH MICROSPHERES

Examiner: B. Forman

Group Art Unit: 1656

CERTIFICATE OF MAILING

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Fern Marder

RESPONSE TO FINAL OFFICE ACTION

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This is in Response to the Office Action mailed May 2, 2001, for the above-identified U.S. Patent Application. This response is timely filed prior to or on the due date of August 2, 2001.

The Assistant Commissioner is hereby authorized to charge any fees, including extension of time fees or other relief as may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our File A-68087-1/RMS/DCF/AMS).

AMENDMENTS

17. (Amended) A method comprising:

a) providing a hybridization complex comprising

i) a first target sequence comprising

1) a first nucleotide at a readout position; and

2) a first label that uniquely identifies said first nucleotide at said readout position;

ii) a capture probe attached to a microsphere on a surface of a substrate, wherein said first target sequence is immobilized on said microsphere by said capture probe; and

b) detecting said label to identify said first nucleotide at said readout position.

18. The method according to claim 17 wherein said first target sequence comprises an adapter sequence and said adapter sequence is hybridized to said capture probe.

19. (Amended) The method according to claim 17 further comprising:

a) providing a second target sequence comprising a first domain and a second domain comprising a detection position;

b) hybridizing a first ligation probe to said first domain and a second ligation probe to said second domain of said second target sequence wherein if said second ligation probe comprises a nucleotide that is perfectly complementary to said nucleotide at said detection position a ligation structure is formed;

c) ligating said ligation structure to form said first target sequence, wherein said readout position is perfectly complementary to said detection position.

20. The method according to claim 19, wherein said first ligation probe comprises an adapter sequence and said second ligation probe comprises said first label.

21. (Amended) The method according to claim 17 further comprising:

a) providing a second target sequence comprising said detection position;

b) hybridizing an extension primer to said second target sequence adjacent to said detection position;

c) adding a polymerase enzyme and at least a first dNTP comprising a covalently attached detectable label under conditions whereby if said first dNTP basepairs with the nucleotide at said detection position, said extension primer is extended by said enzyme to incorporate said label into said extension primer to form said first target sequence.

22. The method according to claim 21, further comprising adding a second dNTP, wherein said first and second dNTPs comprise first and second labels, respectively.

23. The method according to claim 22, wherein at least said first label comprises a fluorophore.

24. The method according to claim 22, wherein at least said first label comprises biotin.

25. The method according to claim 24, wherein at least said first label comprises imine-biotin.

26. The method according to claim 22, wherein said at least said first dNTP comprises a functional group for addition of a fluorophore.

27. The method according to claim 17 further comprising:

a) providing a second target sequence comprising 5' to 3':

i) a first target domain comprising an overlap domain comprising at least a nucleotide in the detection position; and

ii) a second target domain contiguous with said detection position;

b) hybridizing:

i) a first probe to said first target domain; and

ii) a second probe to said second target domain, wherein said second probe comprises:

1) a detection sequence that does not hybridize with said target sequence; and

2) a detectable label;

wherein if said second probe comprises a nucleotide that is perfectly complementary to said detection position a cleavage structure is formed; and

c) contacting said cleavage structure with a cleavage enzyme to cleave said detection sequence to form said first target sequence.

28. The method according to claim 19, 21 or 27, wherein said first target sequence comprises an adapter sequence and said adapter sequence is hybridized to said capture probe.

29. The method according to claim 17, 19, 21 or 27, wherein said substrate is a fiber optic bundle.

30. The method according to claim 17, 19, 21 or 27 wherein said substrate is selected from the group consisting of glass and plastic.

31. The method according to claim 17, 18, 19, 21 or 27, wherein said first label is a fluorophore.

32. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising:

a) providing a hybridization complex comprising:

i) a target sequence; and

ii) at least a first probe, wherein said first probe is hybridized to said target sequence adjacent to said detection position;

b) adding a composition comprising:

i) a nucleotide that hybridizes with the nucleotide at said detection position; and

ii) an enzyme, wherein said enzyme alters said first probe when said nucleotide hybridizes with said nucleotide at said detection position to form an altered probe, wherein said altered probe comprises a label specific to said nucleotide;

c) forming an assay complex by hybridizing said altered probe with a capture probe covalently attached to a microsphere on a surface of a substrate; and

d) determining the nucleotide at said detection position by detecting said label.

33. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising:

a) providing a hybridization complex comprising a target sequence, at least a first probe hybridized with said target sequence adjacent to said detection position, and a capture probe covalently attached to a microsphere on a surface of a substrate;

b) adding a composition comprising a nucleotide that hybridizes with said detection position and an enzyme, wherein said enzyme alters said first probe when said nucleotide hybridizes with said detection position to form

an altered probe, wherein said altered probe comprises a label that uniquely identifies said nucleotide hybridized with said detection position; and

d) determining the nucleotide at said detection position by detecting said label.

34. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising:

a) providing a hybridization complex comprising a target sequence and a capture probe covalently attached to a microsphere on a surface of a substrate, wherein said capture probe hybridizes to said target sequence;

b) adding a composition comprising a nucleotide that hybridizes with said detection position and an enzyme, wherein said enzyme alters said capture probe when said nucleotide hybridizes with said detection position to form an altered capture probe, wherein said altered capture probe comprises a label; and

d) determining the nucleotide at said detection position by detecting said label.

35. The method according to claim 32, 33 or 34, wherein said label is a fluorophore.

36. The method according to claim 32, 33 or 34, wherein said nucleotide is a first dNTP comprising a first label and said enzyme is a polymerase, whereby when said first dNTP basepairs with the nucleotide at said detection position, said first probe is extended by said enzyme to incorporate said first label into said first probe.

37. The method according to claim 32, 33 or 34, wherein said composition comprises a second probe comprising said nucleotide wherein said second probe hybridizes with

said target sequence, said nucleotide basepairs with said detection position and said enzyme is a ligase, whereby when said nucleotide basepairs with said nucleotide at said detection position, a ligation structure is formed and said ligase ligates said ligation structure.

38. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising:

a) providing a hybridization complex comprising said target sequence hybridized with a capture probe, wherein said capture probe is covalently attached to a microsphere on a surface of a substrate; and

b) contacting said hybridization complex with a plurality of detection probes each comprising:

i) a unique nucleotide at a readout position; and

ii) a unique detectable label; and

c) detecting a signal from at least one of said detectable labels to identify the nucleotide at the detection position.

39. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising:

a) providing a hybridization complex comprising said target sequence, wherein said target sequence comprises a first target domain directly 5' adjacent to said detection position, a capture probe covalently attached to a microsphere on a surface of a substrate, and an extension primer hybridized to said first target domain of said target sequence, wherein said capture probe hybridizes with either said extension primer or said target sequence;

b) contacting said hybridization complex with:

i) a polymerase enzyme;

ii) a plurality of dNTPs each comprising a covalently attached detectable label;

under conditions whereby if one of said dNTPs basepairs with the nucleotide at said detection position, said extension primer is extended by said enzyme to incorporate said label; and

c) identifying the nucleotide at said detection position.

40. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence comprising a first target domain comprising said detection position and a second target domain adjacent to said detection position, said method comprising:

a) hybridizing a first ligation probe to said first target domain;

b) hybridizing a second ligation probe to said second target domain, wherein if said second ligation probe comprises a nucleotide that is perfectly complementary to said detection position a ligation structure is formed;

c) ligating said first and said second ligation probes to form a ligated probe;

d) forming a complex with said ligated probe, a capture probe covalently attached to a microsphere on a surface of a substrate, and at least one label;

e) detecting the presence or absence of said label as an indication of the formation of said ligation structure; and

f) identifying the nucleotide at said detection position.

41. (Amended) A method of determining the identification of a nucleotide at a detection position in a target sequence wherein said target sequence comprises 5' to 3':

a) a first target domain comprising an overlap domain comprising at least a nucleotide in the detection position; and

b) a second target domain contiguous with said detection position;

said method comprising:

i) providing a hybridization complex, wherein said hybridization complex comprises:

1) a first probe hybridized to said first target domain; and

2) a second probe hybridized to said second target domain,

wherein said second probe comprises:

i) a detection sequence that does not hybridize with said target sequence; and

ii) a detectable label;

wherein if said second probe comprises a nucleotide that is perfectly complementary to said detection position a cleavage structure is formed;

ii) contacting said hybridization complex with a cleavage enzyme that will cleave said detection sequence;

iii) forming a complex with said detection sequence, a capture probe covalently attached to a microsphere on a surface of a substrate, and at least one label; and

iv) detecting the presence or absence of said label as an indication of the formation of said cleavage structure, whereby the nucleotide at said detection is identified.

REMARKS

Claims 17-41 are pending. Claims 17, 19, 21, 32, 33, 34, and 38-41are amended. Support for the amendment of claim 17 is found throughout the specification as filed, for example at page 11, lines 10-15, p. 3, lines 31-34, p. 12, lines 36-37, p. 42, lines 6-9 and p. 10, lines 24-28. The amendment of claim 19 finds support at p. 4, lines 32-34. Claim 21 is amended for clarity. Support is found throughout the specification

including the figures and the claims. Support for the amendment of claim 32 and claim 33 is found throughout the specification, for example p. 3, line 36 to p. 4, line 5 and in the figures. Support for the amendment of claim 34 is found throughout the specification, for example at p. 4, lines 8-10 and in the figures. Support for the amendment of claim 38 is found throughout the specification, for example at p. 4, line 25 and in the figures. Support for the amendment of claim 39 is found throughout the specification including the figures and claims. Claims 40 and 41 are amended for clarity. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**" For the Examiner's convenience a clean copy of the currently pending claims is appended hereto as Appendix A. Applicants respectfully request entry of the amendments as they put the claims in form for allowance or better form for appeal.

Response to Rejection Under 35 U.S.C. § 112

Claims 17-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the claims "are replete with confusing and contradicting recitations." Specifically, claims 17-31 are indefinite because the claims allegedly do not recite method steps which lead to "detecting." Applicants respectfully traverse the rejection.

In response, Applicants submit that the claims as amended do, in fact, set forth positive, active steps such that the claims are clear. That is, the claims as amended set

forth that the method comprises providing a hybridization complex wherein the first target sequence is hybridized to said capture probe and detecting the label to identify the first nucleotide at the readout position. As such, Applicants submit that the claims clearly set forth the method. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 17-31 are rejected because "specific to" is a relational term but it is unclear whether the "label" relates to the "first nucleotide" and/or "detection position." Applicants respectfully traverse the rejection.

While Applicants do not necessarily agree with the Examiner's characterization of "specific to" , Applicants have amended the claim to recite that the first label "uniquely identifies" the first nucleotide and deleting "specific to." As such, Applicants respectfully request the Examiner to withdraw the rejection.

Claims 17-31 are rejected as indefinite in the recitation "hybridization complex" because it is unclear whether the label is on the target sequence or another member of a complex. Applicants respectfully traverse this rejection.

In response, Applicants submit that both a target sequence and a capture probe are included in the hybridization complex. In addition, claim 17 sets forth that it is the first target sequence that comprises a label that uniquely identifies the first nucleotide at

the readout position. As such, Applicants submit that the claim clearly defines the method. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 19-31 are rejected as indefinite because the claim appears to be a method for making a first target sequence but the relationship between the first target sequence and the second target sequence is not evident. Applicants respectfully traverse this rejection.

The Examiner is correct in noting that the claim describes a method for making a first target sequence. The method includes hybridizing ligation probes to a second target sequence and when a ligation probe comprises a nucleotide that is perfectly complementary to the nucleotide at the detection position of the target sequence, a ligation structure is formed. Once formed, the ligation structure is ligated to form the first target sequence. Within the first target sequence is a readout position that is perfectly complementary to the nucleotide at the detection position. Accordingly, Applicants submit that the claim clearly sets forth the relationship between the first target sequence and the second target sequence. Namely, the second target sequence is a template for the formation of the first target sequence when one of the ligation probes comprises a nucleotide that is perfectly complementary to the detection position. When perfect complementarity exists, the ligation probes are ligated. The product of the ligation reaction is the first target sequence. Applicants respectfully request the Examiner to withdraw this rejection.

Claims 20 and 28-31 are rejected as indefinite because in claim 20 it is unclear how "said first label" relates to the first target sequence. Applicants respectfully traverse this rejection.

Claim 20 depends from claim 19 which in turn depends from claim 17. As set forth in claim 20, the second ligation probe comprises the first label. As set forth in claim 19, when the second ligation probe comprises a nucleotide that is perfectly complementary to the detection position of the target sequence, the ligation structure is formed and the two ligation probes are ligated to form the first target sequence. As set forth in claim 17, the first target sequence comprises the first label. Accordingly, the second ligation probe as set forth in claim 20 initially comprises the label. Upon ligation, the label is incorporated into the first target sequence as set forth in claim 20. Applicants submit, therefore, that the claims in fact, clearly recite the method steps. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 21-31 are rejected as indefinite in the recitations "said detection position" because it is unclear whether the "detection position" is the detection position on the first target sequence or the second target sequence.

In response, Applicants note that the claims have been amended such that detection position in claim 17 has been amended to recite "readout position." Support for readout positions are found at page 11, lines 10-15, wherein it is noted that "the

base which base pairs with a detection position base in a hybrid is termed a "readout position". Applicants respectfully requests the Examiner to withdraw the rejection.

Claims 21-31 are rejected as being indefinite because in claim 21 the relationship between the first target sequence and the second target sequence is not evident.

Applicants note that the claims have been amended to recite that the extension primer is hybridized to the second target sequence, thereby setting forth the relationship between the extension primer and the second target sequence. Upon extension of the extension primer, the first target sequence is formed. Accordingly, Applicants submit that the relationship between the first target sequence and the second target sequence and the second target sequence is, in fact, evident. Applicants respectfully request the Examiner to withdraw this rejection.

Claims 22-26 are rejected as indefinite in claim 22 for the recitation "said first and second dNTPs comprise first and second labels" because it is unclear whether and/or how the "first label" relates to the "first label" of claim 17.

In response, Applicants note that claim 22 depends from claim 21 which in turn depends from claim 17. Claim 21 recites that a first dNTP comprises a detectable label. Clearly, this is the first label as set forth in claim 17. Likewise, the first label as set forth in claim 22 is the first label set forth in claim 17. Accordingly, Applicants

submit that the claims clearly note the method steps and necessary components, i.e., the first label. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 32-37 are rejected as indefinite in claims 32-34, b) because the steps appear to be method steps but the relationship between the "composition" and "altered probe" comprising a label is unclear. Applicants respectfully traverse the rejection.

Applicants note that while the Examiner suggests that claims 32-34 are methods of labeling, Applicants submit the claims are not necessarily limited to methods of labeling. In fact, as the claims point out, the methods include adding a composition that results in altering the probe. While this alteration may include labeling, it does not necessarily require labeling. As such, Applicants submit that the claims clearly define the method. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

Claim 38 is rejected as being indefinite in the recitation of "the readout position" because it lacks proper antecedent basis.

In response, Applicants note that the claim has been amended to perfect the antecedent basis. Applicants respectfully request the Examiner to withdraw the rejection.

Claim 39 is rejected as being indefinite because it is unclear how the "hybridization complex is formed" because the relationship between the capture probe and the target sequence and the extension primer is not defined.

In response, Applicants note that the claim has been amended to recite that the capture probe is hybridized to either the target sequence or the extension primer thereby defining the relationship between the probes.

In addition, the Examiner notes that it is unclear how "contacting said microsphere..." extends the extension primer.

In response, Applicants submit that the claim has been amended to recite contacting said "hybridization complex" instead of contacting said "microsphere." As such, Applicants submit that the claim clearly defines the method. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

Claim 40 is rejected as indefinite in the recitation "forming an assay complex" because it is unclear what method steps are performed in the claimed "assay."

In response, Applicants note that the claim has been amended to delete the term "assay." Accordingly, Applicants submit that the claim clearly defines the method.

Claim 41 also is rejected as indefinite in the recitation "forming an assay complex" because it is unclear what method steps are performed in the claimed "assay."

In response, Applicants note that the claim has been amended to delete the term "assay." Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

Response to Rejection Under 35 U.S.C. § 103

Claims 17-41 are rejected under 35 U.S.C. § 103 as being unpatentable over Nikiforov et al. (U.S. Patent No. 5,679,524, filed August 9, 1996), Walt et al. (6,023,540 and Lyamichev et al. (Nature Biotechnology, March 1999,17: 292-296). The Examiner notes that the claims are rejected for reasons of record in the previous Office Action, mailed 24 August 2000 as applied to new claims 17-41 according to Examiner's best understanding of the claims. However, Applicants note that the Office Action mailed 24 August 2000 set forth two rejections under 103. Former claims 1-12 and 15-16 were rejected under 103 as being unpatentable over Nikiforov et al in view of Walt et al. Claims 13-14 were rejected under 103 as being unpatentable over Nikiforov et al in view of Walt et al and further in view of Lyamichev et al. In contrast, it appears that there is only a single current rejection of all of claims 17-41 under 103 as set forth above. Applicants have attempted to interpret the rejection in light of the rejections set forth in the previous Office Action.

Nikiforov et al. teach the use of immobilized probes that are extended and ligated to determine the nucleotide at a detection position. As acknowledged by the Examiner, Nikiforov (a) does not teach the microspheres on the surface of a substrate.

Walt et al. teaches, among other things, the use of microspheres comprising nucleic acid capture probes on surfaces to detect the presence or absence of nucleic acid sequences. However, Walt et al. does not explicitly teach specific methods for genotyping reactions, e.g. the elucidation of specific nucleotides at specific detection positions.

The Examiner's position appears to be that it would have been obvious for one of ordinary skill in the art to modify the microsphere of Nikiforov et al by positioning the microsphere on a surface wherein each detection position is identified by a unique fluorophore for the expected benefits of "detecting and analyzing a numerous [sic] sequences rapidly and automatically using commercially available software" (see col. 4, lines 20-28 of Walt). Applicants respectfully traverse the rejection.

As the Examiner is aware, a *prima facie* case of obviousness requires that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." (MPEP § 2143).

The requirement that there be some suggestion or motivation to modify or combine references to obtain the claimed invention has not been satisfied in this instance.

The Examiner suggests that the motivation to combine Nikiforov (a) and Walt is "the expected benefit" of detecting numerous nucleotides individually and automatically using commercially available software as taught by Walt (emphasis added). The

Applicants respectfully disagree. As the Examiner is aware, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." M.P.E.P. §2143.01 (emphasis in original). As the Examiner is aware, "obvious to try" is not the standard. The Examiner essentially admits that the motivation is based on "obvious to try", as she states that the benefit is "expected". That is, while Applicants agree that Walt notes that the biosensor disclosed therein can be used with commercially available imaging software, Applicants also submit that Walt is explicitly silent with respect to any teaching or suggestion of methods of using microspheres on a surface of substrate to determine the identification of specific nucleotides at specific detection positions. Moreover, as noted above, Nikiforov fails to teach or suggest microspheres distributed on the surface of a substrate. As noted in M.P.E.P. §2143, "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." To this end, Applicants note that neither Nikiforov nor Walt teach or suggest such a combination. As such, Applicants submit that the Examiner has failed to set forth a prima facie case of obviousness.

Applicants are aware that motivation "for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. (see MPEP 2144,

citing *In re Sernaker*, 702 F.2d 989, 994-5, 217 USPQ 1, 5-6 (Fed. Cir. 1983). However, as noted above, there is no teaching or suggestion of a benefit resulting from the combination of the references that is found in the references themselves. While the Examiner suggests that the benefit is the ability to use commercially available software, Applicants submit that this in no way is a suggestion of a benefit to combine Walt with Nikiforov. Accordingly, Applicants submit that the Examiner has failed to point to any explicit or implicit teaching of the references that suggest a benefit of combining the references. Moreover, Applicants submit that the Examiner has failed to provide a convincing line of reasoning that some advantage would have been produced by the combination. Accordingly, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness.

In addition, Applicants submit that the Examiner has failed to establish a prima facie case of obviousness based on the combination of Nikiforov, Walt and Lyamichev. The Examiner suggests that motivation for the combination is that the nucleotide detection of Nikiforov et al. could be modified "with the hybridization and cleavage of Lyamichev et al. for the expected benefit of quantitative detection of a nucleotide and for the additional benefit of economy of time and labor by eliminating the amplification and primer extension steps as specifically taught by Lyamichev et al.". Applicants respectfully traverse this rejection.

Nikiforov and Walt are described above.

Lyamichev et al teach a method of polymorphism identification that includes a cleavage reaction.

As noted above a *prima facie* case of obviousness requires that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." (MPEP § 2143).

The Examiner suggests that the motivation to combine the references is found in the "expected benefit of quantitative detection of a nucleotide and for the additional benefit of economy of time and labor by eliminating the amplification and primer extension steps as specifically taught by Lyamichev et al.". Essentially, the Examiner's position appears to be that combining the references is motivated by the benefit of quantitative detection without amplification that results in eliminating the primer extension of Nikiforov et al. However, Applicants respectfully remind the Examiner that "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. see MPEP 2143.01 citing *In re Ratti*, 270 F.2d 810,123 USPQ 349 (CCPA 1959).

Applicants submit that to modify the references to "eliminate the primer extension reactions as taught by Lyamichev" operates to change the principle of operation of Nikiforov et al. As such, the teachings of the references are insufficient to render the claims obvious.

Indeed, the intended use of Nikiforov is to perform amplification and extension/ligation reactions to detect nucleic acids. To eliminate the extension reaction would render the teaching of Nikiforov unsatisfactory for its intended purpose. This is impermissible. That is, because the proposed modification would render Nikiforov unsatisfactory for its intended purpose, "then there is no suggestion or motivation to make the proposed modification." (see MPEP 2143.01, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). Accordingly, Applicants submit that the Examiner has failed to set forth a prima facie case of obviousness. Applicants respectfully request the Examiner to withdraw the rejection.

None of the cited references taken alone or in combination renders the claimed invention obvious to one of skill in the art at the time the invention was made. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection should be withdrawn.

CONCLUSION

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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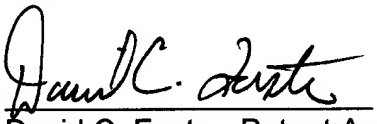

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